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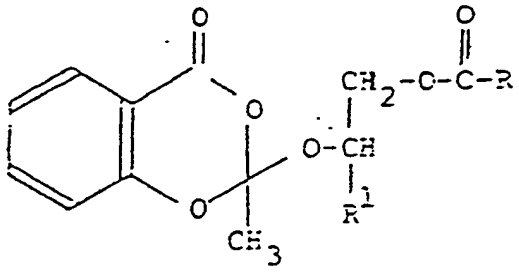

(57) Abstract

An analgesic and anti-inflammatory product comprising a compound having the formula (I), wherein R and R^1 are hydrocarbon radicals and process for the manufacture thereof.

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PHARMACEUTICAL COMPOUND AND PROCESS FOR THE MANUFACTURE THEREOF

BACKGROUND OF THE INVENTION - FIELD OF THE INVENTION AND DESCRIPTION OF THE PRIOR ART

The present invention relates to new pharmaceutical compounds and to a process for the preparation thereof. In particular, the present invention relates to analgesic and anti-inflammatory compounds.

Acetyl salicylic acid, or aspirin as it is more commonly known, is amongst the most widely used of proprietary medicines. Aspirin can be used in the treatment of numerous ailments and is indicated to have analgesic, anti-inflammatory, antipyretic and antirheumatic activity. However, side effects of the drug may limit its application. For example, acetyl salicylic acid may cause gastric irritation and is contra-indicated where such irritation must necessarily be avoided.

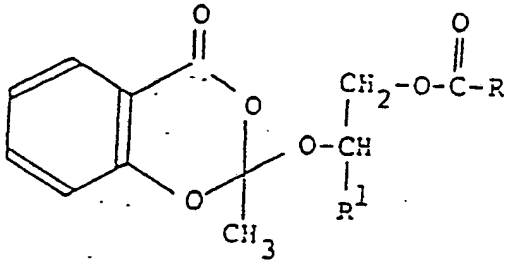
SUMMARY OF THE INVENTION

The object of the present invention is to provide pharmaceutical substances and compositions which exhibit some or all of the advantageous properties of aspirin but in which the contra-indications are minimized.

According to the present invention, it has been discovered that certain esters of acetyl salicylic acid derivatives provide useful pharmaceutical activity.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention provides a compound of the formula I:



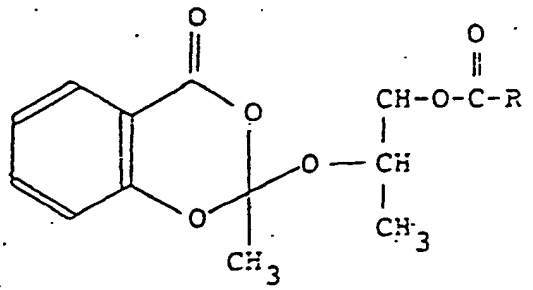
I

In formula I, R and R^1 which may be the same or different, represent any suitable radical, such as a hydrocarbon group.

The present invention further provides pharmaceutically acceptable derivatives thereof and bioprecursors therefor. Pharmaceutically acceptable derivatives thereof may include acid addition salts for example.

In a preferred form R may represent an alkyl group. The alkyl group may include from 1 to 15 carbon atoms. The alkyl group may be a straight chain alkyl group. In a preferred form R represents a straight chained alkyl group of from 7 to 11 carbon atoms. In a preferred form of the invention R^1 represents a lower alkyl group, for example, a methyl, ethyl or propyl group. A methyl group has been found to be most satisfactory.

Thus by way of example the compounds of the present invention may be of the formula II:



II

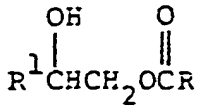
where R is a straight chain alkyl radical having from 1 to 15 carbon atoms and preferably from 7 to 11 carbon atoms.

The compounds of the present invention have analgesic and anti-inflammatory activity similar to those of acetyl salicylic acid. It has been found that the following tests provided a valuable guide to the activity of the compounds of the present invention. These tests are the animal model experiments described by L.B. Witkin et al., J. Pharmacol. Exptl. Therap., 133, 400 (1961) and C.A. Winter et al., Proc Soc, Exp. Biol. Med., 111, 544 (1962). The use of compounds of the formula I is particularly advantageous since gastric irritation associated with acetyl salicylic acid therapy is avoided or at least minimized.

It is to be understood that this invention encompasses the individual isomeric forms of the compounds as well as mixtures thereof. This includes optically active isomers and racemic mixtures thereof. The benzodioxane derivatives of the present invention may be manufactured by any chemical process known to be useful for the manufacture of chemically analagous compounds.

Compounds of the general formula I may be prepared as a mixture of diasteriomers. Such diasteriomers are separable by standard techniques e.g. chromatography.

A preferred process for the manufacture of a benzodioxane derivative of the present invention comprises the reaction of an acetyl salicylic acid derivative with a monoglycol ester of the general formula III:

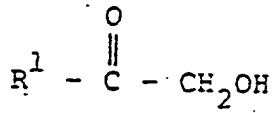


III

wherein R and R^1 have the meanings given above. Standard techniques may be utilized in the reaction between acetyl salicylic acid and the monoglycol esters of formula III for the preparation of

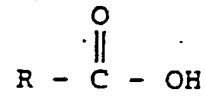
2-alkoxy-4-oxo-1, 3 benzodioxandes as exemplified by C. Ruchardt and S. Rochlitz. Liebigs Ann, Chem., 15 (1974) and G.Y. Paris et al., J. Med. Chem. 23 79 (1980). For example, the acetyl salicylic acid may be activated by conversion to its acylhalide or mixed anhydride to form a 1, 3-benzodioxan-4-one. 1,3-benzodioxan-4-one may be subsequently reacted with monoglycol ester of formula III to produce the compounds of the general formula I. The halide may be selected from a chloride, bromide and iodide. An acid chloride is preferred.

Compounds of the formula III may be prepared via an acylation reaction of a hydroxyketone of the formula IV:



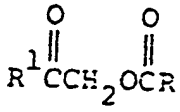
IV

wherein R^1 has the meaning given above; with a carboxylic acid of the formula V:



V

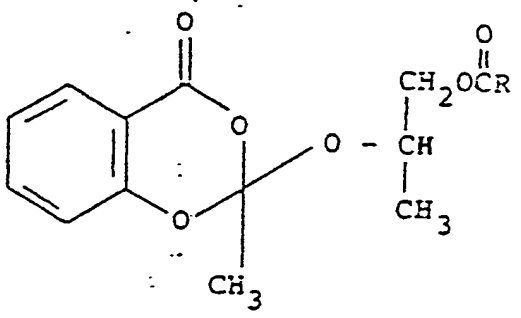
wherein R has the meaning given above; to yield compounds of the formula VI:



VI

A particularly preferred hydroxyketone is the monohydroxy acetone. This yields a monoglycol ester of the formula VII:

This subsequently yields a benzodioxane derivative of the formula II:



II

Particularly preferred compounds of the present invention which exhibit analgesic and anti-inflammatory activity but with reduced gastric irritation include 2-(1-Decanoyloxyprop-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane, 2-(1-Decanoyloxypropyl-2-oxy)-2-methyl-4-oxo-1, benzodioxane, 1-Octanoyloxypropan-2-ol and 2-(1-Octanoyloxyprop-2-oxy)-2-methyl-4-oxo-1,3-benzodioxane.

A suitable acid-addition salt of benzodoxane derivative of the invention is, for example, a salt derived from an organic acid, for example, a hydrochloride, hydrobromide, phosphate or sulphate, or a salt derived from an organic acid, for example an oxalate, lactate, succinate, tartrate, acetate, salicylate, citrate, benzoate, B-naphthoate, or adipate.

The benzodioxane derivatives of the present invention may be administered to animals including man, in the form of a pharmaceutical composition comprising as active ingredient at least one benzodioxane derivative of the present invention, or an acid-addition salt thereof, in association with a pharmaceutically acceptable diluent or carrier therefor. The composition may further comprise a physiologically acceptable excipient, binder, preservative, stabilizer, flavoring or other compounding ingredient. The composition may be prepared in a conventional unit dosage form as called for by accepted pharmaceutical practice. The composition may be included in soft gelatin capsules, two piece hard gelatin shell capsules, tablets, elixirs, suspensions, emulsions or in injectible solutions or suspensions or oily solutions or suspensers.

The amount of active substances included is selected so as to provide an individual unit dosage, preferably from about 30 milligrams to 1500 milligrams of the active ingredient. Other therapeutically valuable substances may also be included. Caffeine, phenacetin, paracetamol may be used in addition to the active ingredient of the present invention.

The following examples are illustrative of the invention, or of intermediates which may lead to the invention, and represent preferred embodiments but are not to be construed as being limitations thereon. All temperatures are in degrees Celsius.

EXAMPLE 1: 1-Decanoyloxypropan-2-one

Monohydroxyacetone was distilled prior to use. Chloroform was distilled from phosphorous pentoxide prior to use. Decanoyl chloride (65 cm^3, 0.3146 mole) was added dropwise to stirred solution of monohydroxyacetone (21.8 cm^3, 0.3146 mole) and anhydrous pyridine (25.4 cm^3, 0.3146 mole) in anhydrous chloroform (500 cm^3). During the addition the solution was maintained in an ice bath. The mixture was then stirred at room temperature overnight. The solution was washed with water (4 x 200 cm^3) and saturated sodium chloride solution (200 cm^3). The organic phase was dried over sodium sulphate and evaporated in vacuo. The resulting oil was distilled to yield 1-decanoyloxypropan-2-one as a mobile liquid, bp 154-60° (1mm) (52.4 g, 0.230 mole, 73%), ir (neat) 2860, 1700, 1400, 1340, 1150, 1110 and 1050 cm^{-1}; pmr ($CDCl_3$) 4.6 (s, 2 H), 2.4 (t, 2 H), 2.1 (s, 3 H), 1.8-1.0 (bm, 14 H) and 0.9 (t, 3 H) ppm.

EXAMPLE 2: 1-Decanoyloxypropan-2-ol

1-Decanoyloxypropan-2-one (44.3 g, 0.194 mole) was dissolved in a solution of tetrahydrofuran (1100 cm^3) and benzene (200 cm^3). After cooling to 5°, ice water (80 cm^3) was added. Sodium borohydride (11 g, 0.291 mole) was added to the stirred solution in small proportions to maintain the temperature at 5°. After addition the reaction was stirred at 5° for 45 minutes and glacial acetic acid (14 cm^3) was added dropwise. Stirring at 5° was continued for a

further 30 minutes. Diethyl ether and chloroform (200 cm^3 each) were added and the mixture washed with water (2 x 200 cm^3), a 1% sodium bicarbonate solution (200 cm^3) and brine (200 cm^3). The organic phase was dried over sodium sulphate and evaporated to yield 1-decanoyloxypropan-2-ol as a colorless liquid (44.0 g, 0.191 mole, 98%), ir(neat) 3600-3100, 2920, 2860, 1730, 1460, 1375, 1240, 1175, 1110, 1055 cm^{-1}; pmr ($CDCl_3$) 4.0 (m, 2 H), 3.6 (m, 2 HO (D_2O m, 1 H), 2.3 (t, 2 H), 2.0-1.0 (bm. 17 H) and 0.85 (t, 3 H) ppm.

EXAMPLE 3: 2-(1-Decanoyloxyprop-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane

Trifluoroacetic anhydride (3.73 cm^3, 0.0263 cm^3) was added to a suspension of 0-acetylsalicylic acid (4.3 g, 0.239 mole) in anhydrous toluene (100 cm^3) at 80°. The solution was stirred at room temperature for 10 minutes. 1-Decanoyloxypropan-2-ol (5 g, 0.0217 mole) in toluene (25 cm^3) was added with rapid stirring. The solution was stirred at room temperature for 5 minutes and in ice for 10 minutes. Pyridine (7 cm^3, 0.0865 mole) was then added. Additional toluene (100 cm^3) was added and the solution extracted with water (2 x 150 cm^3), a saturated sodium bicarbonate solution (3 x 150 cm^3), dried over sodium sulphate and evaporated. The product was chromatographed on silica gel (600 g) in petroleum ether : ether (80:20) and treated with charcoal in acetone to yield 2-(1-decanoyl-oxyprop-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane as a mixture of diasteriomers (6.3 g, 0.0161 mole, 67%); ir (neat) 2920, 2850, 1730, 1600, 1580, 1470, 1380, 1310, 1275, 1250, 1150, 1080, 1015, 920 and 760 cm^{-1}; pmr ($CDCl_3$) 7.9 (dd, 2 H), 7.6-6.8 (m, 3 H), 4.6-3.6 (m, 3H), 2.2 (m, 2 H), 1.85 (s, 3 H), 1.6-1.0 (bm, 17 H) and 0.8 (m, 3 H) ppm.

Anal. calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22%

Found: C, 67.64; H, 8.62%

EXAMPLE 4: 2-(1-Decanoyloxypropyl-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane

A mixture of 1 equivalent of 0-acetylsalicyloyl chloride, 1-decanoyloxypropan-2-ol and anhydrous pyridine in anhydrous,

ethanol free, chloroform was heated at reflux for 24 hours. The solution was washed with water, a 1% sodium bicarbonate solution and evaporated. The product was purified as in Example 3 to yield 2-(1-decanoyloxyprop-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane identical to that in Example 3.

EXAMPLE 5: 1-Octanoyloxypropan-2-ol

By replacing decanoyl chloride in Example with octanoyl chloride, 1-octanoyoxypropan-1-one and subsequently 1-octanoyloxypropan-2-ol, as in Example 2, can be obtained.

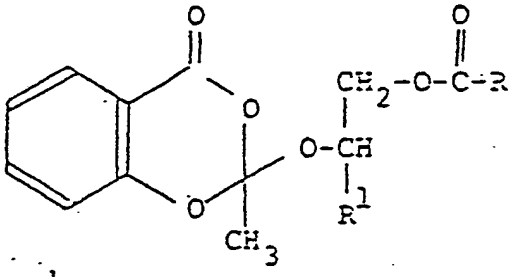
EXAMPLE 6: 2-(1-Octanoyloxyprop-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane

By replacing 1-decanoyloxypropan-2-ol in Example 3 with 1-octanoyloxypropan-2-ol, 2-(1-octanoyloxyprop-2-oxy)-2-methyl-4-oxo-1, 3-benzodioxane can be obtained.

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

CLAIMS:

1. An analgesic and anti-inflammatory compound having the formula:



I

wherein R and R^1 are hydrocarbon radicals.

2. The product of Claim 1 wherein R is an alkyl group having 1 to 15 carbon atoms.

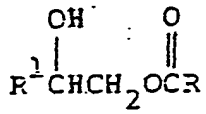
3. The product of Claim 2 wherein said alkyl group is a straight chain alkyl group.

4. The product of Claim 3 wherein said straight chain alkyl group has 7 to 11 carbon atoms.

5. The product of Claim 1 wherein R^1 is a lower alkyl group.

6. The product of Claim 5 wherein R^1 is a methyl, ethyl, or propyl group.

7. A process for preparing an analgesic and anti-inflammatory compound comprising the step of reacting an acetyl salicylic acid derivative with a monoglycol ester having the formula:



III

wherein R and R^1 are hydrocarbon radicals.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/00414

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl 3 C07D 319/08 US Cl. 549/274
A61K 31/365

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols	
US	549/274	260/410.5
	560/66	424/230

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Chemical Abstracts, Volumes 1-97- 1,2-Propanediol, Esters; Glycols, Esters; Antipyretics; Analgesics; Chemical Abstracts-On-Line

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with Indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US,A, 2,070,240, published 9 February 1937 Ruben	1-6
Y	US,A, 2,151,185, published 21 March 1939 Carruthers	1-6
Y	US,A, 3,012,064, published 5 December 1961 Hertling	1-6
Y	US,A, 3,644,424, published 22 February 1972 Sherlock	1-6
Y	US,A, 3,652,665, published 28 March 1972 Shen	1-6
Y	US,A, 3,988,446, published 26 October 1976 Paris	1-6
Y	US,A, 4,046,887, published 6 September 1977 Paris	1-7
Y	Journal of Medicinal Chemistry, Vol.23, No. 1, issued 1980 (Easton, Pennsylvania), Gerard Y. Paris et al., "Glycerides as Prodrugs. 2. 1,3-dialkanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)glycerides (Cyclic Aspirin Triglycerides) as Antiinflammatory Agents", see pp. 79-82.	1-7

* Special categories of cited documents: [15]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
06 June 1983	18 JUL 1983
International Searching Authority [1]	**Signature of Authorized Officer [20]**
RO/US	Norma S. Milestone

Form PCT/ISA/210 (second sheet) (October 1981)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
A	Justus Liebigs Annalen der Chemie, issued 1974 (West Germany), Christoph Ruchardt et al., "Zur ambivalenten Reaktivitat des O-Acetylsalicylsaurechlorids", see pp.15-23.	1-7
A	The Journal of Pharmacology and Experimental Therapeutics, Vol. 133, issued 1961 (Baltimore, Maryland), L.B. Witkl. "Pharmacology of 2-Amino-indane Hydrochloride (SU-8629): A Potent Non-narcotic Analgesic", see pp. 400-408.	1-6
A	Proceedings of the Society for Experimental Biology and Medicine, Vol. III, No. 3, issued December 1962 (Utica, New York), Charles A. Winter et al., "Carrageenin-Induced Edema in Hind Paw of the Rat as an Assay for Antiinflammatory Drugs", see pp. 544-547.	1-6